REMARKS

Status of the claims

Claims 1-5, 22-28 and 30-61 were previously pending. Claims 1, 3, 5, 23, 24, 33-35, 38 and 42-52 have been withdrawn from consideration as a result of restriction and species election requirements dated July 1, 2004 and October 28, 2004.

By virtue of the present response, claims 30, 42 and 56 are amended, and claims 22, 49-51 and 58-61 are canceled without prejudice or disclaimer. Accordingly, claims 1-5, 23-28, 30-48 and 52-57 are pending and claims 2, 4, 25-28, 30-32, 36, 37, 39-41 and 53-57 are under consideration.

Entry of the amendment after final rejection is proper since claim 30 has been amended by incorporating the limitation provided by previously pending dependent claim 22. Claim 56 has been placed in independent form and independent claims 58-61 have been canceled. Thus, no new search or consideration is needed.

In addition, the incorporation of the limitation of claim 22 into claim 30, and the cancellation of claims 58-61, renders moot the pending rejections under 35 U.S.C. § 102(b) based upon Green, Miesfeld, and Abeliovich (in regard to claims 2, 4, 26-28, 30-32, 54 and 55), the rejection under 35 U.S.C. § 102(a) based upon Hori, the rejection of claims 25, 36 and 39-41 under 35 U.S.C. § 103(a) based upon Green and Pomerantz and the rejection of claims 25, 36, 39-41 and 55 under 35 U.S.C. § 103(a) based upon Green in view of Barbas. Furthermore, the amendments simplify the issues involved with the rejection under 35 U.S.C. § 112, first paragraph (written description).

Restriction and rejoinder

Applicants reiterate their argument, presented in a response dated May 19, 2005, that claim 30 (of Group II) is a linking claim, linking the proteins of Group I (which are encoded by the polynucleotide of claim 30) with the methods of Group III (which utilize the polynucleotide of claim 30). The arguments presented in the Office Action dated November 15, 2005, to the effect that claim 30 is not a linking claim, are traversed inasmuch as the isolated polynucleotide of claim 30 both encodes the proteins of Group I and is used in the methods of Group III. Moreover, method claims 42-51 (Group III)

contain all of the limitations of claim 30, and should be rejoined and examined upon allowance of claim 30.

In addition, Applicants note that, with respect to engineered zinc finger proteins, the Office has previously determined that concurrent search and examination of nucleic acids and proteins does not impose a serious burden. *See* co-owned application serial No. 10/651,761 Decision on Petition dated March 30, 2005. Accordingly, Groups I and II should be rejoined.

Finally, it appears that the Examiner has already searched and examined the full scope of the pending claims. As stated by the Examiner, the elected subject matter is Group II drawn to nucleic acid, a DNA target sequence, the target located in a plant cell and a maize C1 activation domain.[1] However, claim 30 is subject to a rejection under the written description requirement of 35 U.S.C. § 112, first paragraph, based upon the full scope of the claim. Previous claim 30, which was not limited to a DNA target sequence, the target located in a plant cell and a maize C1 activation domain, was the subject of multiple anticipation rejections based upon references that did not describe the target located in a plant cell or a maize C1 activation domain. Further, the Examiner separately rejected claims such as claim 25 under 35 U.S.C. § 103(a) that were not limited to the elected subject matter. Thus, given the nature and substance of the examination the claims have undergone, rejoinder is appropriate.

35 U.S.C. § 112, first paragraph: Written description

Claims 2, 4, 25-28, 30-32, 36, 37, 39-41 and 53-56 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement.[2] Office Action at pages 3-9. The Office Action acknowledges that cysteine and histidine residues (as recited in independent claims 30 and 56) are known to coordinate a zinc atom in a zinc finger, but cites Green for the proposition that the zinc coordinating cysteine and histidine residues are not predictably interchanged, because

[1] Office Action, June 14, 2006, page 2.

[2] Claims 22 and 58-61 were also rejected under this section but, inasmuch as those claims have been canceled, the rejection is moot.

conversion of finger 2 alone, or combinations of fingers 1 and 3 or fingers 2 and 3, of Zif268 to a C_4 finger abolish DNA binding.

"The 'written description' requirement serves a teaching function...in which the public is given 'meaningful disclosure in exchange for being excluded from practicing the invention for a limited period of time.'" *University of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 922, 69 USPQ2d 1886, 1891 (Fed. Cir. 2004) (citation omitted). Another "purpose of the 'written description' requirement is . . . [to] convey with reasonable clarity to those skilled in the art that, as of the filing date [ ], [the applicant] was in possession of the invention." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). *See also Enzo Biochem Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 1329, 63 USPQ2d 1609, 1617 (Fed. Cir. 2002). The requirement is satisfied when the specification "set[s] forth enough detail to allow a person of ordinary skill in the art to understand what is claimed and to recognize that the inventor invented what is claimed." *University of Rochester*, 358 F.3d at 928, 69 USPQ2d at 1896. Whether or not a specification satisfies the requirement is a question of fact, which must be resolved on a case-by-case basis (*Vas-Cath*, 935 F.2d at 1562-63, 19 USPQ2d at 1116), and it is the examiner's "initial burden [to] present[ ] evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims" (*In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976)).

"[A]pplicants have some flexibility in the 'mode selected for compliance' with the written description requirement" (*University of Rochester*, 358 F.3d at 928, 69 USPQ2d at 1896); it is well settled that actual reduction to practice is not necessary to satisfy the requirement (*id.*, at 926, 69 USPQ2d at 1894). "The inquiry for adequate written description simply does not depend on a particular claim format, but rather on whether the patent's description would show those of ordinary skill in the [relevant art] that the inventors possessed the claimed invention at the time of filing." *Union Oil Co. v. Atlantic Richfield Co.*, 208 F.3d 989. 997-998, 54 USPQ2d 1227, 1233 (Fed. Cir. 2000), cert. denied, 533 U. S. 915 (2001). Whether the level of disclosure in the specification would have allowed one skilled in the art to recognize that the inventor

invented what is claimed is a question of fact. The USPTO has summarized a number of factors to be considered in making this determination; they include "the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention." Guidelines for Examination of Patent applications Under 35 U.S.C. § 112, ¶ 1, "Written Description" Requirement, 66 Fed. Reg. 1099, 1106 (Jan. 5, 2001). "Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." *Id.*

Applicants traverse the rejection and supporting remarks. As previously stated,[3] all members of the genera embodied by the pending claims are clearly and adequately described. Indeed, the Office has previously acknowledged that the skilled artisan can clearly envision the proteins encoded by the claimed nucleic acids and that the relevant sequences of all claimed species have been disclosed. For example, in the Office Action dated December 23, 2005, at page 5, the Examiner states:

> . . . one of skill in the art could envision every single amino acid change to the primary amino acid sequence represented by the formulas within the specification and claims.

Given that the Office agrees that all claimed species are adequately described, the written description rejection appears to be based on the contention that not every substitution of a zinc coordinating residue will result in adoption of a ßßa structure, or will generate a protein capable of binding DNA. However, such contentions do not provide sufficient basis to support a written description rejection.

Moreover, Applicants note that polynucleotides encoding proteins that do not adopt a ßßa structure, and polynucleotides encoding proteins that do not bind DNA, are not encompassed by the claims (see, *e.g.*, claim 30). Thus, in using such contentions as

[3] Response dated December 5, 2005 at pages 2-4

the basis for a rejection, the Examiner is improperly reading structural and functional limitations out of these claims.

It is noted that the rejection focuses on what is allegedly exemplified in the application instead of considering the application disclosure as a whole. For example, the Examiner states that "[a] review of the specification identified multiple examples of only one general type of non-canonical zinc finger protein meeting the claim limitations: a zinc finger protein in which the zinc coordinating residues are C2HC. There does not appear to be a description of any other zinc fingers that meet the claim limitations with regard to zinc coordinating residues and secondary structure." Office action, page 7. However, as noted above, it is well settled that actual reduction to practice is not necessary to satisfy the written description requirement. *University of Rochester*, 358 F.3d at 926, 69 USPQ2d at 1894.

The Examiner next asserts that "the specification does not describe a structure function correlation for residues that support the formation of the claimed secondary structure when a zinc coordinating residue is altered." *Id.* While not entirely clear, it appears that the examiner's concern is that when a zinc coordinating residue is altered in order to form a non-canonical zinc finger component the resulting zinc finger protein may not contain an alpha helix as recited in claim 30. However such a concern is not an issue under the written description requirement of this section of the statute. Here, the plain language of the claims requires that the non-naturally occurring zinc-finger binding proteins encoded by the claimed polynucleotides contain the stated structure including the specified alpha helix. Thus, if one designs a polynucleotide encoding a zinc finger binding protein by altering a zinc coordinating residue and the resulting encoded protein does not contain the required structure, the polynucleotide that encodes that protein is not within the scope of the claims.

The Examiner also expresses concern that the "specification does not describe which zinc finger proteins are definitively non-naturally occurring because all natural proteins are not known." *Id.*, page 8. The Examiner also indicates that natural proteins include proteins that result from naturally occurring mutations. *Id.* The Examiner concludes that the specification must provide characteristics that allow one to distinguish

between the isolated polynucleotide molecules that encode non-natural proteins from those that encode natural proteins. *Id.* This concern is directed to whether one can readily determine the metes and bounds of the language used in claim 30, *i.e.*, how does one distinguish between polynucleotides that encode naturally occurring zinc-finger binding proteins and those that encode non-naturally occurring zinc-finger proteins. Such concerns are properly addressed under the second paragraph of this section of the statute, not the written description requirement. In any event, the Examiner's concern presupposes that a specific polynucleotide is under consideration. If the polynucleotide under consideration encodes a zinc finger protein that naturally occurs, it is not within the scope of claim 30 as that claim is limited to "isolated polynucleotides encoding a non-naturally occurring zinc-finger protein...." Thus, a person of ordinary skill in the art can readily discern, now or at any time in the future, the metes and bounds of claim 30.

In regard to claim 56, in addition to the arguments set forth above, it is noted that claim 57 that depends from claim 56 is not included in this rejection. In relevant part, claim 56 requires the "two amino-terminal zinc coordinating residues are cysteine residues, one of the carboxy-terminal zinc coordinating residues is a histidine residue and one of the carboxy-terminal zinc coordinating residues is a cysteine residue" while claim 57 further limits this aspect of claim 56 by stating the "carboxy-terminal zinc coordinating histidine residue is amino terminal to the carboxy-terminal zinc coordinating cysteine residue." Thus, it is seen that in relevant part claim 56 is setting forth two alternatives for the carboxy terminal zinc coordinating residues with claim 57 explicitly reciting one of the two possibilities. Since claim 57 is not subject to the written description rejection, the rejection should be withdrawn in regard to claim 56 since claim 56 only further includes in relevant part the second alternative to that set forth in claim 57.

Thus, when properly construed with all limitations considered, the claims are adequately described, as set forth above and acknowledged by the Office. Accordingly, the rejection should be withdrawn.

35 U.S.C. § 102

As discussed above, the amendment to claim 30 and the cancellation of claims 58-61 render the section 102 rejections based upon Green, Miesfeld and Hori moot. In addition, these amendments render moot the anticipation rejection based upon Abeliovich in regard to claims 2, 4, 26-28, 30-32, 54 and 55. Thus, the only anticipation rejection which needs to be discussed is that of claims 56 and 57 based upon Abeliovich.

Abeliovich

Anticipation is an exacting standard. Under 35 U.S.C. § 102, every limitation of a claim must identically appear in a single prior art reference for it to anticipate the claim. *In re Bond*, 910 F.2d 831, 832, 15 USPQ2D 1566, 1567 (Fed. Cir. 1990). Implicit in a review of an examiner's anticipation analysis is that the claim must first have been correctly construed to define the scope and meaning of each contested limitation. See, e.g., *In re Paulsen*, 30 F.3d 1475, 1479, 31 USPQ2D 1671, 1674 (Fed. Cir. 1994) ("To properly compare [an allegedly anticipatory prior art reference] with the claims at issue, we must construe the term 'computer' to ascertain its scope and meaning.").

Here claim 56 requires that the polynucleotide encodes a "non-naturally-occurring zinc finger binding protein." In describing Abeliovich, the Examiner states that the polypeptide encoded by $\lambda_{1\text{-}5/6}$ is a "non-naturally occurring fusion protein comprising CCHC zinc fingers and beta-galactosidase." OA, page 15. While the fusion protein of Abeliovich noted by the Examiner is non-naturally occurring, it is composed of the naturally occurring zinc finger binding protein, UMS-specific single-stranded DNA-binding protein (UMSBP) from *C. fasciculata*. *Id.*, paragraph bridging pages 7766-67. Thus, any protein described in Abeliovich that includes UMSBP, including fusion proteins, necessarily includes a naturally occurring zinc finger protein, not a non-naturally occurring zinc finger binding protein as required by claim 56.

The fusion proteins that can be encoded by the claimed polynucleotides include a non-naturally occurring zinc finger binder protein and are *further* composed of another moiety such as an activation domain. This is seen in claim 39 which depends from claim 30, "[a]n isolated polynucleotide according to claim 30 *further* encoding a functional

domain." (emphasis added). Thus, the fusion proteins that are encoded by the present polynucleotides differ from the fusion protein described in Abeliovich relied upon by the Examiner.

The Examiner recognizes that Abeliovich does not state that UMSBP contains the beta turn and alpha helix required by claim 56. However, the Examiner has shifted the burden to Applicants to determine the structure of UMSBP citing *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977). OA, page 15. The evidence that UMSBP does not contain the beta turn and alpha helix set forth in claim 56 is found in Abeliovich itself.

Abeliovich states that analysis of the nucleotide sequence shows a reading frame that encodes a zinc finger protein of the CysXXCysXXXXHisXXXXCys class ($CX_2CX_4HX_4C$ or X_4 motif). *Id.*, paragraph bridging pages 7766-67. Abeliovich also states that a high similarity is found between the UMSBP zinc fingers and those found in the sequences of *L. major* HEXBP, citing Webb[4] and noting that both UMSBP and HEXBP are "DNA-binding proteins that bind specifically to G-rich, single-stranded sequences." *Id.*, page 7769, right hand column. Webb states that, in contrast to the TFIIIA-type zinc finger, the CCHC-containing peptide from the HIV-1 NCP revealed that the CCHC motif "represents a structurally unique class of zinc finger, having a much more compact structure with extensive internal hydrogen bonding and no a-helices" and that "[c]onservative substitution of several positions within the motif indicate that this structure is likely shared by all CCHC consensus zinc finger motifs," referencing Figure 3. *Id.*, paragraph bridging pages 14000-01 (citation omitted). Figure 3 of Webb sets forth a comparison of the CCHC motifs of HEXBP and other nucleic acid binding proteins having the X_4 motif (including NCP, which is identified as HIV-1 in the figure). Since Abeliovich states that UMSBP has the X_4 motif, it is reasonable to conclude that UMSBP does not have an alpha helix.

Additional evidence exists that X_4 zinc binding proteins as described in Abeliovich are distinct from the zinc-finger binding proteins encoded by the

[4] Webb *et al.* (1993) *J. Biol. Chem*, **268**:13994-14002; attached to Information Disclosure Statement filed herewith

polynucleotides of claim 56. For example, Pabo[5] first cautions that "the term 'zinc finger' has acquired a loose—almost topological—definition and has been used when referring to almost any sequence that has a set of cysteines and/or histidines within a short region of a polypeptide chain." *Id.*, page 1069. Pabo indicates that TFIIIA-type zinc fingers will be discussed along with zinc fingers that are "structurally homologous" with the TFIIIA fingers. *Id.* Pabo then indicates that "other" cysteine-rich and histidine-rich motifs, including certain retroviral proteins are discussed later. *Id.* This later discussion states that the retroviral proteins have the CCHC/X_4 motif. *Id.*, paragraph bridging pages 1079-1080. Thus, persons of skill in this art do not consider zinc binding proteins having the X_4 motif such as those described in Abeliovich to be structurally homologous to the zinc finger binding proteins encoded by the polynucleotides of claim 56.

For these reasons, the rejection is improper and should be withdrawn.

The examiner responded to applicants' previous arguments for novelty over Green by alleging that the term "engineered," as applied to the proteins recited in the claims, encompasses modifications other than rational design and empirical selection as set forth in the specification. Office Action, pp. 18-21. The examiner concluded that "the features upon which applicant relies (i.e., the alteration in nucleotide binding specificity) are not recited in the rejected claim(s)." Office Action, p. 20. In fact, and contrary to the examiner's conclusion, the claims recite a protein that "is engineered to bind to a target sequence." Claim 30(ii). The term "engineered" is stated to refer to proteins whose structure and composition result from rational criteria such as substitution rules and algorithms as described, *e.g.*, in WO 00/42219 (designed ZFPs) and proteins whose production results primarily from an empirical process such as phage display as described, for example, in U.S. patents 5,789,538; 6,007,988; and 6013453; and in WO 95/19431; WO 96/06166 and WO 98/54311 (selected ZFPs). Specification at page 10, lines 17-29. Thus, the examiner's conclusion, reproduced above, indicates that she has

[5] Pabo *et al.* (1992) Ann. Rev. Biochem. 61: 1053-1095; Reference C100 of Information Disclosure Statement mailed on May 9, 2005; reviewed by examiner on November 12, 2005

not correctly construed the claims. Moreover, substitution of a zinc-coordinating residue, as disclosed by Green, is neither a rational design process, nor an empirical selection process, for engineering a protein to bind to a chosen target sequence.

For this reason as well, the rejection should be withdrawn.

35 U.S.C. § 103

The Office Action contains three rejections under this section of the statute: claims 25, 36 and 39-41 based upon Green and Pomerantz, claims 22 and 37 based upon Green, Pomerantz and Guyer and claims 25, 36, 39-41 and 55 based upon Green and Barbas III.

Since claim 30 has been amended to include the limitation of claim 22, *i.e.*, the target sequence is in a plant cell, the rejection of claim 22 will be addressed first.

Claim 22

a. The rejection

Green discloses construction of mutants of zif268 in which each of the three constituent zinc fingers was converted from its naturally-occurring C_2H_2 (CCHH) configuration to a C_4 (CCCC) configuration. Green also constructed mutants of zif268 in which both fingers 1 and 3, and fingers 2 and 3, were converted to the C_4 configuration. The Office states that Green discloses polynucleotides encoding mutated zif268 proteins in which, in the first or third finger, one of the C-terminal zinc-coordinating residues is a cysteine, and that these mutated zif268 proteins were engineered to bind to the wild-type zif268 target sequence. The Office also states that Green provides indirect evidence that his mutated zif268 proteins adopted a ßßa structure, based on their ability to bind DNA. Office Action at paragraph bridging pages 11-12.[6]

[6] Applicants assume that the references to "Chen et al" on page 11 of the Office Action actually denote the Green et al. reference, as no "Chen et al." reference is listed on any PTO-892 or Information Disclosure Statement present in Applicants' copy of the file, and Green *et al.* is the only reference cited in the § 102 rejection. **For the second time**, applicants request clarification.

Pomerantz is stated to disclose design of a polynucleotide encoding an artificial transcription factor DNA binding domain fused to a VP16 transcriptional activation domain.[7] *Id.* Pomerantz is also stated to disclose *in vivo* assays of his artificial transcription factor in which binding to promoter sequences was assayed. *Id.*

The examiner first concludes on the basis of Green and Pomerantz that "[i]t would have been obvious...to modify the polynucleotide and target sequence of Green [] to include the VP16 activation domain and the location of the target site in the promoter as taught by Pomerantz....." Office Action, page 22.

The Examiner builds upon this conclusion by relying upon Guyer for its description of a GAL4 DNA binding domain fused to a maize C1 transcription activation domain (*id.*, paragraph bridging pages 23-24) and concluding that it would have been obvious to "modify the polynucleotide to comprise the C1 activation domain...and to use a plant cell comprising the modified zif268 cognate DNA binding site...." *Id.*, page 24.

The so-called motivation to make these changes to the prior art is stated to be "in order to receive the expected benefit of determining whether the modified zif268 transcription factor taught by Green [] is capable of specifically binding its target sequence in vivo in a plant cell thus expanding the number of species in which the modified zif268 transcription factor can be used." *Id.*, page 25. The Examiner also notes that Guyer teaches that proteins from different kingdoms may be combined to create hybrid transcription factors for use in plants, and that these hybrid transcription factors may provide specific gene activation in plants. *Id.* Finally, the Examiner asserts that motivation to use a modified zif268 DNA binding domain in a plant cell is found in Guyer teaching that "proteins from different kingdoms may be combined to create hybrid transcription factors for use in plants, and that these hybrid transcription factors may provide specific gene activation in plants." *Id.*

[7] Applicants note that, subject to a species election requirement, the C1 activation domain had been elected. *See* page 9, *supra*, of this Response.

b. The rejection is based upon hindsight and an impermissible obvious to try standard

"It is well-established that before a conclusion of obviousness may be made based on a combination of references, there must have been a reason, suggestion, or motivation to lead an inventor to combine those references." *Pro-Mold and Tool Co. v. Great Lakes Plastics Inc.*, 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629-30 (Fed. Cir. 1996). As stated in *In re Kotzab*, 217 F.3d 1365, 1369, 55 USPQ2d 1313, 1316 (Fed. Cir 2000):

> A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. See [In re] *Dembiczak,* 175 F.3d 994 at 999, 50 USPQ2D [1614] at 1617 [Fed. Cir. 1999]. Close adherence to this methodology is especially important in cases where the very ease with which the invention can be understood may prompt one "to fall victim to the insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher." Id. (quoting *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 USPQ. 303, 313 (Fed. Cir. 1983)).

The court went on to state "[p]articular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed." *Kotzab*, 217 F.3d at 1371, 55 USPQ2d at 1318.

Furthermore, as explained in *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (citations omitted):

> The admonition that "obvious to try" is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. ...In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general

guidance as to the particular form of the claimed invention or how to achieve it.

It is believed that the Examiner's case is based upon hindsight and falls under the impermissible "obvious to try" standard and thus is in error.

Green and Guyer are key to this rejection. Green describes that the C2H2 motif of the naturally occurring zinc finger protein zif268 can be changed to a C4 motif, and the resultant protein is sometimes able to recognize DNA in a manner identical to the wild-type protein. As recognized by the Examiner, the work described in Guyer involves the use of a hybrid transcription factor that uses GAL4 as the DNA binding domain and a synthetic promoter that comprises ten GAL4 binding sites. Office Action, page 24; Guyer, Figure 1. In contrast, claim 30 (incorporating the limitation of previous claim 22) requires that the protein is engineered to bind to a target sequence in a plant cell. This concept is exemplified in Example 7 of the present specification where "[m]odified zinc finger proteins were designed to recognize various target sequences in the *Arabidopsis* GMT gene (GenBank Accession Number AAD38271)."

A first example of the hindsight nature of this rejection is seen in the Examiner's statement that the so-called motivation to combine the references in the proposed manner is to determine "whether the modified zif268 transcription factor taught by Green [] is capable of specifically binding its target sequence *in vivo* in a plant cell." *Id.* page 25. However, it has long been held that motivation to combine references must be practical instead of being based upon abstract, theoretical or academic considerations. *See In re Stemniski,* 444 F.2d 581, 170 USPQ 343 (1971).

At best, the Examiner's motivation would result in an academic experiment using modified zif268 having a C4 motif and the known DNA binding site of zif268, a mammalian protein. This is not what claim 30 requires. The polynucleotide of claim 30 is one that encodes a protein that has been engineered to bind to a target sequence that is in a plant cell. Furthermore, this academic exercise is just that and does not provide the requisite motivation.

Furthermore, Green does not suggest the use of his modified zif268 proteins in plants. Guyer suggests that other activation domains be fused to the GAL-4 DNA-

binding domain (*Id.*, page 638, left hand column, third full paragraph), but provides no suggestion of using other DNA-binding domains in his hybrid transcription activators. Thus, neither Green nor Guyer suggest the use of a modified zif268 in a plant cell as asserted by the Examiner. This is evidence the Examiner's rejection is based upon hindsight.

The Examiner's statement that use of modified zif268 proteins in a plant cell "may" provide specific gene activation in plants points to the use of an impermissible obvious to try standard. "An 'obvious-to-try' situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued." *In re Eli Lilly & Co.*, 902 F.2d 943,945, 14USPQ2d 1741, 1743 (Fed. Cir. 1990) (citation omitted). The Examiner's so-called motivation (to discover "whether the modified zif268 transcription factor taught by Green et al is capable of specifically binding to its target sequence *in vivo* in a plant cell. . .," emphasis added) is based upon supposition and speculation instead of being grounded in facts set forth in the relied-upon prior art.

For these reasons, the rejection is improper and should be withdrawn.

Claims 25, 36 and 39-41.

Claims 25, 36 and 39-41 stand rejected as allegedly obvious over Green in view of Pomerantz (Office Action at pages 21-23). Green and Pomerantz are cited as above. Pomerantz is also stated to disclose *in vivo* assays of his artificial transcription factor in which binding to promoter sequences was assayed. *Id.*

Applicants traverse the rejection and supporting remarks.

As noted above, Green fails to disclose or suggest the claimed polynucleotides encoding zinc finger proteins that are engineered to bind to a target sequence in a plant. Pomerantz fails to cure this deficiency, disclosing only two naturally-occurring, C_2H_2 zinc fingers from zif268 fused to a naturally-occurring Oct-1 homeodomain. Thus, Pomerantz's fusion protein is, first of all, not a zinc finger binding protein, as claimed,

since it also contains a homeodomain. Secondly, the zinc finger portion of Pomerantz's protein is not engineered to bind a target sequence in a plant, consisting merely of two naturally-occurring zinc fingers from zif268, a mammalian protein. Thus, neither Green nor Pomerantz disclose or suggest zinc finger proteins that are engineered to bind to a target sequence in a plant; accordingly, their combination also fails to disclose or suggest polynucleotides that encode engineered zinc finger proteins as required by claim 30. For these reasons, the rejection is improper and should be withdrawn.

Claim 37

Claim 37 also stands rejected as allegedly obvious over Green in view of Pomerantz and further in view of Guyer.

In relevant part, claim 37 requires that the polynucleotide of claim 30 further encodes the maize C1 activation domain. Guyer describes a polynucleotide that encodes GAL4-maize C1 fusion protein. *See, e.g.,* Figure 1. However, as set forth above in regard to claim 30, the combined disclosures of Green and Guyer do not render obvious the subject matter of claim 30. Therefore these references do not suggest the subject matter of claim 37, which depends from claim 30. For these reasons, the rejection is improper and should be withdrawn.

Claims 25, 36, 39-41 and 55

Claims 25, 36, 39-41 and 55 stand rejected as allegedly obvious over Green in view of Barbas (Office Action at pages 25-27). Green is applied as above. Barbas is stated to disclose "expanded" zinc finger proteins to which additional fingers have been added, mutagenized expanded zinc finger proteins, expanded zinc finger proteins fused to dimerizaton domains and activation domains, and activation of transcription from a promoter.

Applicants traverse the rejection and supporting remarks.

As noted above, Green fails to disclose or suggest the claimed polynucleotides encoding zinc finger proteins that are engineered to bind to a target sequence in a plant cell. Barbas, for its part, discloses only C2H2 zinc finger proteins (see, for example,

independent claims 1, 14, 22, 28 and 49 of Barbas). Being so limited, Barbas teaches away from combining his disclosure with that of Green's C_4 zinc finger protein, or indeed with the disclosure of any non-C2H2 zinc finger protein. For these reasons, and those set forth above in regard to claim 30, there is no motivation to combine the disclosures of Green and Barbas. Accordingly, the rejection should be withdrawn.

CONCLUSION

In light of the amendments and remarks presented herein, it is believed that the elected subject matter is in condition for allowance. Applicants therefore request examination of generic subject matter. If the Examiner believes that a telephone conversation would expedite prosecution, she is invited to contact the undersigned (Brennan), using the contact information given below.

Respectfully submitted,

Date: May 10, 2007

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